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(54) OPHTHALMIC COMPOSITION BASED ON NEUROTROPHIC FACTOR

(57) Abstract:

PROBLEM TO BE SOLVED: To prepare the subject composition, capable of reducing the intraocular tension and promoting the functional maintenance, improvement, growth and regeneration of an optic nerve and useful as a therapeutic agent, etc., for glaucoma or cerebral central lesions by mixing one or more of specific neurotrophic factors.

SOLUTION: This ophthalmic composition is prepared by mixing one or more of (A) a neurotrophic factor NGF (derivative) and (B) a neurotrophic factor BDNF (derivative). The composition is capable of specifically binding to only a neurotrophic factor receptor of a nerve and manifesting the objective effects. Thereby, the composition can directly be administered to eyeballs and further systemically administered and formulated into an ophthalmic ointment, an eye drop, an intraocular injection, an internal agent, a medicine for intravenous, intramuscular or subcutaneous injection, a contact lens absorbent, etc., for use.

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**Translation:**

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**DETAILED DESCRIPTION**

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[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to the contact lens which comes to blend this with the glaucoma remedy list using the constituent for ophthalmology and it by the neurotrophic factor. Moreover, by eyeball administration, it plans so that the brain central lesion according the constituent for ophthalmology by this neurotrophic factor to intracranial transport may be treated from an optic nerve.

[0002]

[Description of the Prior Art] 30-40 40 or older-year persons' people are told that the symptoms of glaucoma develop by one person today. Since this glaucoma is increasing every year and it is becoming the grave problem of an aging society, establishment of the therapy approach of the glaucoma which is not until now has important semantics, and an effective remedy to this glaucoma is desired.

[0003] Here, glaucoma is generated in order to be pressed by the optic disk whose optic nerve is the gate of an eyeball since intraocular pressure goes up, consequently to start a functional disorder.

[0004] It was only that an old glaucoma therapy lowers intraocular pressure by instillation of beta-blocker, or oral administration of an intraocular pressure depressant. However, even if it lowers intraocular pressure, a low vision and tunnel vision advance continuously, and even if it prescribes vitamin B12, a blood-flow improvement agent, etc. for the patient, it may be unable to protect. Moreover, it is inadequate just to lower intraocular pressure and the drugs which manage functional maintenance of the optic nerve itself, an improvement and growth, and playback are required of it.

[0005]

[Means for Solving the Problem] The constituent for ophthalmology by the neurotrophic factor of this invention which solves the above-mentioned technical problem is characterized by coming to mix one sort of these derivatives, or two sorts or more in a neurotrophic factor NGF and a neurotrophic factor BDNF list.

[0006] Moreover, the constituent for ophthalmology by the 1st neurotrophic factor is characterized by being a glaucoma remedy.

[0007] It is the nerve growth factor in which the above-mentioned glaucoma remedy has nervous differentiation and a survival maintenance operation with a neurotrophic factor NGF family and its derivative, and they are NGF, BDNF, a ciliary nerve nutritional factor (CNTF), and neuro-tropine. - 3 (NT-3), neuro-tropine - It is characterized by coming to mix any one sort of 4/5 (NT-4/5) and the neuro-tropine -6 (NT-6), or two sorts or more.

[0008] The above-mentioned glaucoma remedy is characterized by being the drugs for subconjunctival injections, the drugs for eyeball injection, the drugs for the injection in an eye (injection in a vitreous body etc.), the drugs for instillation, an oral administration agent, ointment, the drugs for intravenous injections, intramuscular medication, and the drugs for subcutaneous injections.

[0009] It is characterized by blending or absorbing and becoming the constituent of a contact lens about the above-mentioned glaucoma remedy.

[0010] The constituent for ophthalmology by the above-mentioned neurotrophic factor is characterized by being the lesion remedy of an optic nerve own [, such as \*\*\*\* optic neuritis and a neuritis optica axialis, ].

[0011] The constituent for ophthalmology by the above-mentioned neurotrophic factor is characterized by being the remedy of the optic nerve disorder by the remedy of the ophthalmic-nerve-function failure by the optic nerve pressure by optic canal fracture or the neoplasm in an eye socket, or the artery varix, an intracranial disease, the brain tumor, the hypophyseal tumor, bleeding, and infarction.

[0012] It is the nerve growth factor in which the above-mentioned remedy for ophthalmology has nervous differentiation and a survival maintenance operation with a neurotrophic factor NGF family and its derivative, and they are NGF, BDNF, a ciliary nerve nutritional factor (CNTF), and neuro-tropine. - 3 (NT-3), neuro-tropine - It is characterized by coming to mix any one sort of 4/5 (NT-4/5) and the neuro-tropine -6 (NT-6), or two sorts or more.

[0013] The brain central lesion remedy of this invention comes to mix one sort of these derivatives, or two sorts or more in a neurotrophic factor NGF and a neurotrophic factor BDNF list, and is characterized by treating the lesion of the brain center by the axonal transport of an optic nerve by administration to the eyeball of this neurotrophic factor.

[0014] It is the nerve growth factor in which the above-mentioned brain central lesion remedy has nervous differentiation and a survival maintenance operation with a neurotrophic factor NGF family and its derivative, and they are NGF, BDNF, a ciliary nerve nutritional factor (CNTF), and neuro-tropine. - 3 (NT-3), neuro-tropine - It is characterized by coming to mix any one sort of 4/5 (NT-4/5) and the neuro-tropine -6 (NT-6), or two sorts or more.

[0015]

[Embodiment of the Invention] Hereafter, the gestalt of operation of this invention is explained.

[0016] When the constituent for ophthalmology by the neurotrophic factor of this invention comes to mix one sort of these derivatives, or two sorts or more in a neurotrophic factor NGF and a neurotrophic factor BDNF list and uses them for them as a glaucoma remedy especially, it is effective.

[0017] Moreover, it is the nerve growth factor which has nervous differentiation and a survival maintenance operation with a neurotrophic factor NGF family and its derivative further in the above-mentioned glaucoma remedy, and they are NGF, BDNF, a ciliary nerve nutritional factor (CNTF), and neuro-tropine. - 3 (NT-3), neuro-tropine - The thing which comes to mix any one sort of 4/5 (NT-4/5) and the neuro-tropine -6 (NT-6) or two sorts or more can be used.

[0018] Here, the above-mentioned neurotrophic factor (NGF) is also called the nerve growth factor, and is discovered by REVIMON Tartini of Italy. This neurotrophic factor is protein which performs maintenance growth of a nerve cell, and differentiation, and NGF and BDNF are these one.

[0019] In this invention, using these NGF(s), BDNF(s), NGF families, etc., the constituent for ophthalmology is offered and effect is taken to a glaucoma therapy or its prevention.

[0020] Here, since it combines only with a nervi-nervorum nutritional factor receptor specifically and the above-mentioned neurotrophic factor demonstrates effectiveness, as a result, it does not have a side effect, and an eyeball can also be directly medicated with it, and it can also perform whole body administration.

[0021] When using the constituent for ophthalmology of this invention as for example, partial pharmaceutical preparation for ophthalmology, it can also use as an eye ointment. Moreover, the constituent for ophthalmology of this invention can be used for the various eye drops suitably adjusted using the basis generally used, for example, an eye perfusate agent, ophthalmic solutions, the injections in an eye, \*\*\*\* injections, etc. Moreover, the constituent for ophthalmology of this invention can also be used as an oral administration agent, ointment, the drugs for

intravenous injections, intramuscular medication, and drugs for subcutaneous injections in addition to the above.

[0022] Moreover, when using as ophthalmic solutions or a contact lens absorption administration agent, \*\*\*\*\* and in order to carry out adjustment soon at an aqueous humor presentation, various additives permitted pharmacologically, such as an isotonizing agent and a buffer, can be added if needed. Although the pharmacology effectiveness can be heightened as this additive by specifically adding kinds, such as grape sugar, a sodium chloride, potassium chloride, a calcium chloride, magnesium sulfate, a sodium hydrogencarbonate, and a glutathione, or two sorts or more, this invention is not limited to these as an additive. In addition, as an example of an additive, "BSS Plus" can be mentioned, for example.

[0023] Although aquosity ophthalmic solutions, nonaqueous nature ophthalmic solutions, suspensibility ophthalmic solutions, milkiness ophthalmic solutions, etc. can be mentioned when using the instillation constituent in this invention as a glaucomatous remedy for example, this invention is not limited to these. As glaucoma applied to this invention, although low tension glaucoma (normal tension glaucoma), hypertonia-bulbi glaucoma (open-angle glaucoma or narrow-angle glaucoma (acute-inflammation nature glaucoma), native glaucoma, and sequence-glaucoma), etc. can be mentioned, this invention is not limited to this and takes effect in all kinds of glaucoma.

[0024] Here, an example of the above-mentioned ophthalmic solutions is explained below.

[0025] Generally, manufacture of ophthalmic solutions may be divided roughly and the case where an aquosity solvent is used, and a nonaqueous nature solvent may be used. As the above-mentioned aquosity solvent, sterilization purified water, a physiological saline, BSS Plus, etc. can be mentioned, for example. Moreover, as the above-mentioned nonaqueous nature solvent, vegetable oil, such as cotton seed oil, soybean oil, sesame oil, and peanut oil, etc. can be mentioned, for example. To these solvents, ophthalmic solutions are manufactured for a neurotrophic factor NGF, neurotrophic factors BDNF, these families, etc. a kind or by two or more sorts' responding to the object, and dissolving or suspending an initial complement.

[0026] Under the present circumstances, to the above-mentioned solvent, an isotonizing agent, pH regulator, a viscous agent, a suspending agent, an emulsifier, a preservative, and the thing by which pharmacological allowance is carried out can be added as an additive if needed.

[0027] Here, as the above-mentioned isotonizing agent, a sodium chloride, a boric acid, a potassium nitrate, D-mannitol, grape sugar, etc. can be mentioned, for example.

[0028] As the above-mentioned pH regulator, a boric acid, dried sodium sulfite, a hydrochloric acid, a citric acid, a sodium citrate, an acetic acid, potassium acetate, a sodium carbonate, a borax, etc. can be mentioned, for example.

[0029] As the above-mentioned viscous agent, methyl cellulose, hydroxypropylcellulose, polyvinyl alcohol, sodium chondroitin sulfate, a polyvinyl pyrrolidone, etc. can be mentioned, for example.

[0030] As the above-mentioned suspending agent, polysorbate 80, polyoxyethylene hydrogenated castor oil 60, polyoxy hydrogenated castor oil, etc. are mentioned, for example.

[0031] Yolk lecithin, polysorbate 80, etc. can be mentioned as the above-mentioned emulsifier.

[0032] As the above-mentioned preservative, a benzalkonium chloride, benzethonium chloride, chlorobutanol, phenyl ethyl alcohol, a paraoxybenzoic acid, etc. can be mentioned, for example.

[0033] Moreover, glaucomatous therapy and prevention can be performed, carrying out a contact lens by blending or absorbing the glaucoma remedy of this invention to the constituent of a contact lens.

[0034] Moreover, the neurotrophic factor of this invention can be used besides glaucoma. For example, you may make it use the constituent by the above-mentioned neurotrophic factor as a lesion remedy of an optic nerve own [, such as \*\*\*\* optic neuritis and a neuritis optica axialis, ].

[0035] Moreover, you may make it use as a remedy of the ophthalmic-nerve-function failure by the optic nerve pressure by optic canal fracture or the neoplasm in an eye socket, or the artery varix in addition to the remedy for ophthalmology. Moreover, it is effective also in the therapy of the optic nerve disorder by bleeding and infarction, an intracranial disease, and others, for example, a hypophyseal tumor. [ brain tumor ]

[0036] Moreover, since an optic nerve nutritional factor acts on an optic nerve, and is incorporated by eyeball partial administration of instillation etc. and the constituent by the neurotrophic factor of this invention is transported to intracranial by the axonal transport (active) of an optic nerve, an optic nerve nutritional factor demonstrates the curative effect of a brain central lesion.

[0037] For this reason, it is effective in various kinds of cranial nerve disease therapies which start apoptosis, such as Alzheimer, a demyelination nervous disease, an autoimmune disease, the cerebral hemorrhage, cerebral infarction, a brain tumor, an encephalopathy, brain injury, aging, the therapy of other intracranial lesions, Parkinson's disease, multiple sclerosis, amyotrophic lateralsclerosis, etc.

[0038] Furthermore, there is effectiveness in the therapy of paralysis of the limbs which happen for the phonation disorder encountered as a result of various brain lesions, dysosmia, the dyskinesia, sensory disturbance, general paralysis, and hemiplegia, the dysbasia or disturbance of consciousness, a memory disorder, and dotation etc. Moreover, effectiveness is to bring forward a rehabilitation therapy and many functional recovery, and a bedridden elderly can be lessened. Consequently, social rehabilitation will be brought forward and it will be useful to aging prevention.

[0039] The medication method of the constituent of this invention can be performed like the various eye drops suitably adjusted using the basis generally used, for example, an eye perfusate agent, ophthalmic solutions, the injections in an eye, \*\*\*\* injections, etc. Moreover, the constituent of this invention can also be used as an oral administration agent, ointment, the drugs for intravenous injections, intramuscular medication, and drugs for subcutaneous injections in addition to the above.

[0040]

[Example] Although the example which shows the effectiveness of this invention is explained hereafter, this invention is not limited to this.

[0041] In this example, the experiment which checks the effectiveness of a neurotrophic factor to the optic nerve disorder in glaucoma was conducted. Here, it is thought that glaucoma is generated in order to start a functional disorder, since an optic nerve is pressed by increased intraocular pressure by the optic disk which is the gate of an eye. At this example, while raising intraocular pressure using a colored rabbit, making optic nerve disorder start, decreasing the light reflex of the pupil to stimulus light and performing measurement of this, eyewash was applied in a neurotrophic factor NDF and BDNF (for 4 times per and one month day), and the curative effect of a neurotrophic factor was checked by performing the progress comparison with natural neglect.

[0042] The path of the light reflex of a pupil serves as the eye -> optic nerve

(centripetalism way) -> central -> parasympathetic nerve (centrifugal way) -> iris, and the failure of the above-mentioned optic nerve turns into a centripetalism way failure, and appears as lowering of the light reflex. In this example, the direct reaction of the light reflex of the pupil by the side of a luminous stimulus and \*\* was observed.

[0043] In this example, in order to raise intraocular pressure, the ring-like strong cornea aspirator was created. If the ring aspirator of the above is applied to the strong cornea section of a buttock outside and is attracted, lock out of a buttock will take place and intraocular pressure will go up. This is the well-known approach used for the ophthalmodynamometer etc. in an ophthalmology field. Using "EC5000Aspiration Unit (trade name)" made from NIDEKU as the above-mentioned suction pump, the buttock exterior was able to be attracted by the negative pressure of 70cmHg, and intraocular pressure was able to be raised to 60mmHg(s).

[0044] In the stimulus light source for light-reflex measurement, it is Neitz Brite Scope. It used. The convex lens of +14D was placed before it at the distance of 7cm, the inside of an eye was illuminated with the light which condensed once and was diffused, it was made open-loop (open loop), and the large range of eyegrounds was irradiated uniformly. In this example, it was made the thing of the eye of a rabbit for which light is irradiated a little from a lower part, and the light reflex of maximum (max) is measured. Record was performed using "macropolaphy auto6 (trade name)" by the Polaroid company. Using the above-mentioned increased-intraocular-pressure equipment, luminous-stimulus equipment, and this pupil diameter mensuration, the optic nerve disorder by increased intraocular pressure was judged, and the judgment experiment of the curative effect of a neurotrophic factor was conducted.

[0045] First, it drew in with the strong limbus aspirator, intraocular pressure was raised to 60mmHg(s), and light-reflex measurement by the side of an experiment eye and \*\* was performed weekly.

[0046] At the time of the eating and drinking which will supply food to a rabbit in the morning and an afternoon twice on the 1st, attraction was stopped by a unit of 1 hour.

[0047] Although decrease of the light reflex was hardly accepted to stimulus light at one week and two-week attraction, it began to accept from the 3rd week. It was interrupted by attraction for one month, and progress of light-reflex change was observed (for one month). Although it recovered little by little even if it carried out natural neglect, in the example of administration, the remarkable restorative effect was respectively seen 1 4 times per day in a neurotrophic factor NGF and BDNF.

[0048] The curative effect by the neurotrophic factor showed up in one week, and the ophthalmic nerve function was gradually recovered with time amount progress.

[0049] Although immediate effect nature had the direction of NGF administration, BDNF was also behind [ NGF ] in effectiveness a little strongly, and the restorative effect showed up.

[0050] Eye drops were adjusted in this example, using a neurotrophic factor NGF and BDNF as a reagent. Using the above-mentioned neurotrophic factor NGF and BDNF, it dissolved in commercial BBS plus (made in Al Cong), and eye drops were made. Various electrolyte ion, a buffer, an isotonizing agent, a glutathione, a glucose, etc. are contained in this BBS plus. It is useful to eyeball protection and drug effect is raised.

[0051] In this example, concentration of a neurotrophic factor was set to 10micro g/250ml, and prepared the instillation reagent. In addition, that what is necessary is not to be limited to g/250ml with a concentration [ of the instillation reagent mentioned above ] of 10micro, and just to adjust suitably according to the object and pharmaceutical form, even if the above-mentioned concentration is 0.1micro g-100mg / about 250ml, the effectiveness of this invention discovers it.

[0052] The medication method of eye drops carries out dropping administration - [one drop of ] every several drops once 4 times per day after pressure release. This dropped drug solution is attracted from a cornea, and shifts to anterior sac underwater, that part demonstrates validity in a nerve fiber toward the optic disk from croquette tubing, and a part is diffused in a vitreous body and results in an optic nerve. Moreover, the part results in an optic nerve through unconventional route (the circuit in an eye where anterior sac water results in choroid-suprachoroidal space through the iris and a ciliary body in addition to usual conventional route discharged from a buttock is checked from a series of researches using the various markers of Bill.A and others.) of anterior sac water, and demonstrates validity. Thereby, it is checked in this invention that instillation is effective. In addition, it is checked that the above-mentioned circuit in an eye exists also in a rabbit by colo and others (exp.eye.res 23:57-585).

[0053] In this example, it asked for whenever [ recovery ] by raising intraocular pressure, having lengthened the value of the pupil diameter which shows the light reflex which pressed the optic nerve for four weeks (about one month), measured the light reflex immediately after pressure release, and was recovered with time amount progress by making the pupil diameter at this time into a reference value from the reference value, and having used light-reflex variation as \*\*gamma. This result is shown in drawing 1.

[0054] Although the example of natural neglect was also in the recovery inclination as shown in drawing 1, it checked that the ophthalmic solutions of NGF by this invention expressed effectiveness at an early stage, and the ophthalmic solutions of BDNF had the strong pharmacology effectiveness.

[0055] From this result, it was checked that a neurotrophic factor NGF and BDNF have a curative effect to the optic nerve disorder by glaucoma.

[0056]

[Effect of the Invention] As mentioned above, as explained to the detail with the gestalt and example of operation, since it combines only with a nervi-nervorum nutritional factor receptor specifically and the constituent for ophthalmology by this invention demonstrates effectiveness, as a result, it does not have a side effect, and can carry out direct administration at an eyeball, and can also perform whole body administration. especially the instillation constituent of this invention has a curative effect to the optic nerve disorder boiled and depended on glaucoma, and is useful in pharmacology.

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## CLAIMS

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[Claim(s)]

[Claim 1] The constituent for ophthalmology by the neurotrophic factor characterized by coming to mix one sort of these derivatives, or two sorts or more in a neurotrophic factor NGF and a neurotrophic factor BDNF list.

[Claim 2] The glaucoma remedy with which the constituent for ophthalmology by the neurotrophic factor of claim 1 is characterized by being a glaucoma remedy.

[Claim 3] It is the nerve growth factor in which a glaucoma remedy according to claim 2 has nervous differentiation and a survival maintenance operation with a neurotrophic factor NGF family and its derivative, and they are NGF, BDNF, a ciliary nerve nutritional factor (CNTF), and neuro-tropine. - 3 (NT-3), neuro-tropine - Glaucoma remedy characterized by coming to mix any one sort of 4/5 (NT-4/5) and the neuro-tropine -6 (NT-6), or two sorts or more.

[Claim 4] The glaucoma remedy with which a glaucoma remedy according to claim 2 or 3 is characterized by being the drugs for subconjunctival injections, the drugs for eyeball injection, the drugs for the injection in an eye, the drugs for instillation, an oral administration agent, ointment, the drugs for intravenous injections, intramuscular medication, and the drugs for subcutaneous injections.

[Claim 5] The contact lens characterized by blending or absorbing and becoming the constituent of a contact lens about a glaucoma remedy according to claim 2 or 3.

[Claim 6] The remedy for ophthalmology with which the constituent for ophthalmology by the neurotrophic factor of claim 1 is characterized by being the lesion remedy of an optic nerve own [, such as \*\*\*\* optic neuritis and a neuritis optica axialis, ].

[Claim 7] The remedy for ophthalmology characterized by the constituent for ophthalmology by the neurotrophic factor of claim 1 being the remedy of the optic nerve disorder by the remedy of the ophthalmic-nerve-function failure by the optic nerve pressure by optic canal fracture or the neoplasm in an eye socket, or the artery varix, an intracranial disease, the brain tumor, the hypophyseal tumor, bleeding, and infarction.

[Claim 8] It is the nerve growth factor in which the remedy for ophthalmology according to claim 6 or 7 has nervous differentiation and a survival maintenance operation with a neurotrophic factor NGF family and its derivative, and they are NGF, BDNF, a ciliary nerve nutritional factor (CNTF), and neuro-tropine. - 3 (NT-3), neuro-tropine - Remedy for ophthalmology characterized by coming to mix any one sort of 4/5 (NT-4/5) and the neuro-tropine -6 (NT-6), or two sorts or more.

[Claim 9] The brain central lesion remedy which comes to mix one sort of these derivatives, or two sorts or more in a neurotrophic factor NGF and a neurotrophic factor BDNF list, and is characterized by treating the lesion of the brain center by the axonal transport of an optic nerve by administration to the eyeball of this neurotrophic factor.

[Claim 10] It is the nerve growth factor in which a brain central lesion remedy according to claim 9 has nervous differentiation and a survival maintenance operation with a neurotrophic factor NGF family and its derivative, and they are NGF, BDNF, a ciliary nerve nutritional factor (CNTF), and neuro-tropine. - 3 (NT-3), neuro-tropine - Brain central lesion remedy characterized by coming to mix any one sort of 4/5 (NT-4/5) and the neuro-tropine -6 (NT-6), or two sorts or more.

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[Translation done.]

*[drawing not available with machine translation]*